Articles

Human T-Lymphotropic Virus Type I Seroprevalence Among Japanese Americans

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The epidemiology of human T-lymphotropic virus type I (HTLV-I) infection is not well defined in Japanese Americans. This impairs using approaches that could reduce viral transmission and monitor carriers for the disease. Using enzyme-linked immunosorbent assay and p21e recombinant Western blot testing, HTLV-I antibody was measured in unlinked samples from Japanese-American patients at 4 physicians' offices in San Francisco, California. Of 442 patients, 4 (0.9%; 95% confidence interval 0.25%, 2.3%) were confirmed seropositive, all with an HTLV-I rather than an HTLV-II pattern on Western blot. Seroprevalence was highest among the issei or immigrant generation (3/230 or 1.3%) compared with the second-generation nisei (1/191 or 0.5%) or third-generation sansei (0 of 17). Prevalence did not differ by age or sex, although the number of positive subjects in each subgroup was small. Of 88 patients with familial origins in endemic areas of southern Japan, none were seropositive. In this sample of Japanese Americans, HTLV-I seroprevalence was lower than in residents of endemic southern Japan but higher than among American blood donors. The prevalence was most similar to that in nonendemic areas of Japan. The public health implications of HTLV-I infection among Japanese Americans are discussed.

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Human T-lymphotropic virus type I (HTLV-I) is a human oncovirus discovered in the early 1980s[1] that causes adult T-cell leukemia[2,3] and HTLV-I–associated myelopathy/tropical spastic paraparesis[4,5] in a minority of those infected with the virus. It is transmitted by sexual intercourse,[6] by blood transfusion,[7,8] and from seropositive women to their offspring with 20% to 30% efficiency, primarily through breast-feeding.[9]

Infection with HTLV-I is prevalent in southern Japan and the Pacific islands, several Caribbean countries, and central Africa.[10] In Hawaii, HTLV-I seroprevalence of 20% has been reported in middle-aged Japanese-American men of Okinawan descent.[11] The prevalence of the virus, however, among the large population of Japanese Americans living in the western continental United States has not been studied.

Because persons infected with HTLV-I may be screened medically for HTLV-I–associated diseases and because changes in breast-feeding and sexual behavior can interrupt transmission of the virus, we studied HTLV-I prevalence among Japanese-American patients at four medical practices in San Francisco.

Patients and Methods

Population and Procedures

The study population consisted of all Japanese-American patients presenting for office visits and laboratory tests between February 7 and December 27, 1990, to four San Francisco physicians. These physicians were selected because their practices had high proportions of Japanese-American patients. Each physician reviewed the ethnicity of all patients seen during the study period.

For all patients with Japanese-American ancestry who required blood specimens for clinical laboratory tests, the physician filled out a brief data sheet. Information was obtained on age, sex, generation of residence in the United States, and whether either maternal or paternal family origins were in HTLV-I–endemic areas of Kyushu, Shikoku, or Okinawa. (This last item was added after the beginning of the survey, and data were not collected on about 25% of respondents.) Each data sheet was marked with a subject identification number, which also appeared on a set of labels that were attached to the laboratory requisition forms and the blood specimen tubes. Thus, although the data sheet and blood specimens

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ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
HTLV-I = human T-lymphotropic virus type I

were marked with the subject identification number, no link to a patient's identity was maintained, and informed consent was not obtained. The patient's medical record was marked after enrollment to preclude duplicate entry into the study. The study protocol was approved by the Committee on Human Research of the University of California, San Francisco.

Measurement of HTLV-I Antibodies

Clinical laboratories performing laboratory tests for the four physicians separated serum and plasma from blood specimens marked with the study labels and saved

TABLE 1.—*Demographic Characteristics of the Study Population**

Characteristic	Men, No. (n = 179)	Women, No. (n = 258)	All Patients, No. (N = 442)
Age, yr			
20-29	3	5	8
30-39	11	5	17
40-49	19	18	37
50-59	33	47	80
60-69	43	70	115
≥70	68	112	182
Generation of US Residence			
Issei (immigrant)	74	153	230
Nisei (2nd generation)	95	94	191
Sansei (3rd generation)	10	7	17
Unknown	0	4	4
Area of Origin in Japan			
Kyushu	17	20	37
Shikoku	12	16	28
Okinawa	0	1	1
Endemic, unspecified†	8	14	22
Other part of Japan	85	125	215
Unknown	10	3	13
Missing data	47	79	126

*Data for sex were missing from the data sheets of 5 patients and for age of 3 patients.
†Responded positively to question on origin in any of Kyushu, Shikoku, or Okinawa but did not specify which area.

the refrigerated specimens. On a weekly basis, specimens and data sheets were collected and brought to the study laboratory. Antibodies to HTLV-I were measured by enzyme-linked immunosorbent assay (ELISA, Dupont, Wilmington, Del), and specimens with absorbance values greater than 70% of the manufacturer's recommended cutoff were retested in duplicate. If the levels were still above 70% of the cutoff, the specimens were tested by the p21*env*-enhanced Western blot method (Cambridge Biotech, Rockville, Md). Specimens with reactivity to both *gag* (p19 or p24) and *env* (p21e or gp46) HTLV-I proteins were considered positive.

Statistical Analysis

The 95% confidence intervals on prevalence were calculated using the exact binomial method. Subgroup-specific seroprevalence using information from the data sheet was analyzed with the SAS-PC (SAS, Cary, North Carolina) software on a personal computer.

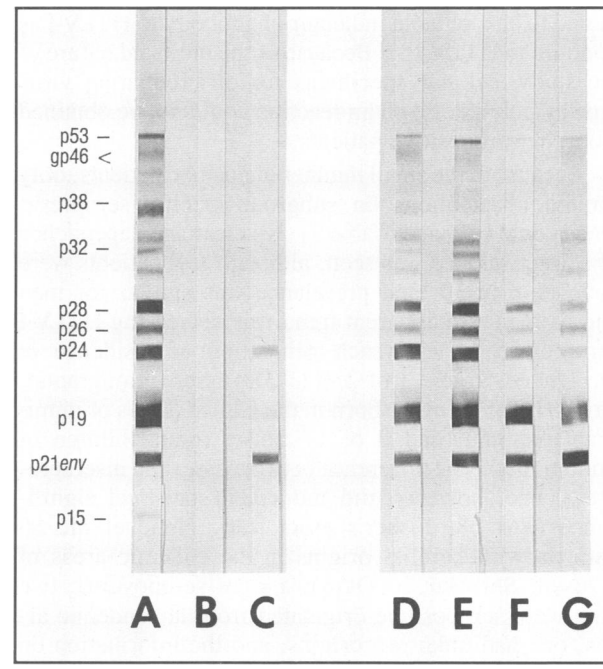

Figure 1.—We performed p21*env*-enhanced Western blot testing on blood specimens taken from Japanese Americans seropositive for human T-lymphotropic virus type I (HTLV-I). Lane A shows the HTLV-I–positive control serum exhibiting reactivity with multiple viral proteins as labeled by molecular weight. Lane B is a negative control, and Lane C is an HTLV-II–positive control serum. Lanes D through G are specimens from positive patients, all of which show p19 reactivity equal to or greater than p24 reactivity, consistent with HTLV-I antibody.[12]

Results

Study Population

Data sheets and blood specimens were available for 536 patients. On initial review of the data, 94 patients were determined to be Japanese citizens residing temporarily in San Francisco. None of these patients were HTLV-I–seropositive, and they were excluded from subsequent analysis. Table 1 shows the demographic characteristics of the 442 Japanese Americans in the study population. Women comprised 59% of the sample, and the age distribution was skewed toward older patients. Consistent with the older age of the patients, most were either issei (immigrants) or nisei (children of immigrants), with only 17 sansei (grandchildren of immigrants) in the sample. Data on familial origin in Japan were not obtained for 126 patients because this question was added to the questionnaire after enrollment had begun; origin was unknown for 13. Of the remaining 303 patients, 88 (29%) had family origins in the southern Japanese areas of Kyushu, Shikoku, or Okinawa where HTLV-I is endemic.

Seroprevalence

Of the 442 patients, 4 had repeatedly reactive ELISA results, and all 4 (0.9%, 95% confidence interval 0.25%, 2.3%) were confirmed seropositive by p21*env*-enhanced Western blot testing. All 4 seropositive specimens were at least as reactive to the HTLV-I p19 *gag* protein as to the p24 *gag* protein (Figure 1).[12] This pattern has been determined to be a reliable indicator of antibody to HTLV-I as opposed to HTLV-II.[12] Because of the unlinked nature of the study, cellular specimens for differentiating virus type by polymerase chain reaction could not be obtained from the seropositive patients.

Because of the small number of positive patients, only limited observations on subgroup-specific seroprevalence could be made (Table 2). No clear age dependence of seroprevalence was seen, although few patients were younger than 40, and prevalence was similar for men and women. An apparent trend was decreasing HTLV-I seroprevalence with each generation of residence in the United States: 3 of 230 (1.3%) issei (immigrants), 1 of 191 (0.5%) nisei (born in the United States of immigrant parents), and 0 of 17 sansei (grandchildren of immigrants). The difference between issei and nisei seroprevalence, however, did not reach statistical significance ($P = .38$, Fisher's exact test). None of the 88 patients with familial origins in the endemic areas of Kyushu, Shikoku, or Okinawa were seropositive; two who were seropositive originated from nonendemic areas, one had unknown origins, and the information on this variable was unavailable for the fourth seropositive person.

Discussion

Because of the relatively small sample size of the study, the confidence intervals on our 0.9% HTLV-I seroprevalence estimate for Japanese Americans (0.25%, 2.3%) are large; nevertheless, comparison may be made with other published values. In the endemic area of Kyushu, southern Japan, 8% of blood donors were HTLV-I-seropositive compared with 0.8% of blood donors in other areas of Japan.[13] In contrast, only 0.025% of US blood donors were HTLV-seropositive, although rates were higher in certain localities.[14] Caution must be exercised in comparing data from published studies because of different laboratory techniques and dissimilar ages of the patients in view of the strong age dependence of HTLV-I seroprevalence. For this study we used a sensitive and specific testing method[15] but had a clinic-based sampling frame and a preponderance of older patients, both of which may have inflated true prevalence rates.

Most studies have reported lower HTLV-I seroprevalence in immigrants than in the endemic populations from which they emigrated. Tajima and colleagues studied migrants aged 16 through 39 years from endemic Kyushu who were workers at a company in nonendemic Aichi prefecture and found an overall prevalence of 4%,[16] a rate not much lower than that to be expected among similarly aged residents of Kyushu. Blattner and coworkers studied Okinawan immigrants to Hawaii and found an overall seroprevalence of 20% among middle-aged to elderly men participating in a cardiovascular disease survey.[11] Rates of antibody positivity were correlated with length of childhood residence in endemic areas, and these rates increased with age even among nisei, leading the authors to hypothesize latent infection with subsequent antibody production. Ho and associates suggested that intermarriage and a higher socioeconomic status might account for the lower prevalence among immigrants.[17] Tsugane and colleagues studied Japanese immigrants to Bolivia and found HTLV-I seroprevalence of 17% in first-generation and 6% in second- or third-generation Japanese immigrants.[18] Prevalence was significantly higher among immigrants from Kyushu or Okinawa than among those from nonendemic areas of Japan.

The reasons for a lower HTLV-I seroprevalence among immigrants from endemic areas are complex. Maintenance of a stable prevalence of HTLV-I infection in a population probably requires transmission by the mother-to-child and sexual routes plus more uncommon vectors, such as contaminated blood transfusions or needles.[19] Whereas mother-to-child infection may continue in immigrants, the sexual and blood-transfusion modes of transmission become less important than in the endemic area because the sexual partner or blood donor is far less likely to be HTLV-I-infected in the adopted country, assuming cultural integration between the immigrant minority and the host country. Because mother-to-child transmission is only about 20% efficient and because only infected women will transmit the virus to the next

TABLE 2.—*Human T-Lymphotropic Virus Seroprevalence in San Francisco Japanese Americans by Age, Sex, Generation of United States Residence, and Area of Origin in Japan**

	No. Positive	(%)	No. Tested	P Value
Age, yr				
10-49	1	(1.6)	62	
50-69	1	(0.5)	195	
≥70	2	(1.1)	182	.95†
Sex				
Male	2	(1.1)	179	
Female	2	(0.8)	258	.81‡
Generation of US Residence				
Issei	3	(1.3)	230	
Nisei	1	(0.5)	191	.38‡
Sansei	0	(0.0)	17	
Unknown	0	(0.0)	4	
Area of Origin in Japan				
Kyushu, Shikoku, or Okinawa	0	(0.0)	88	
Other part of Japan	2	(0.9)	215	.50‡
Unknown	1	(7.7)	13	

*Data for age (3 patients), sex (5 patients), and area of origin (126 patients) were missing from data sheets.
†Mantel-Haenszel χ^2 test.
‡Fisher's exact test was done between first 2 categories.

generation through that route, prevalence should diminish notably over the first few generations in the new country.

The existence of a cohort effect on HTLV-I age-specific seroprevalence rates has also been postulated.[20] Ueda and co-workers demonstrated falling age-specific seroprevalence for cohorts of 20- to 30-year-old women between 1966 and 1988.[21] According to this hypothesis, lower HTLV-I prevalence in more recent cohorts may be at least in part the result of life-style changes that affect transmission efficiency, such as increased bottle-feeding of infants or an increased use of condoms for contraception. Finally, the existence of environmental cofactors that increase the risk of HTLV-I infection or seroconversion has been suggested.[11,22] These poorly defined factors, such as lower socioeconomic class, other infectious disease, or vector-borne infection, might be more common in an endemic area than in the host country and thus would lead to a lower prevalence of HTLV-I antibody among immigrants. Little experimental evidence exists for latent infection or vector transmission, and, although socioeconomic status has been associated with seropositivity, sociologic rather than environmental factors are more likely responsible for the association.

In conclusion, we observed a prevalence of antibodies to HTLV-I among Japanese-American patients that was lower than that in endemic areas of Japan; however, a larger study is needed to obtain more precise age- and sex-specific prevalence estimates. The decline in prevalence with the number of generations of residence in the United States is consistent with data from other studies and is probably due to a lower transmission of the virus by sexual and parenteral routes. A larger study of HTLV-I prevalence among pregnant Japanese-American women would be useful in determining the cost-effectiveness of a program aimed at screening such women for HTLV-I antibody and discouraging breast-feeding by those who are seropositive. The efficacy of such an intervention in reducing transmission from 30% to 3% has been clearly demonstrated in Japan.[23]

Pending a better estimation of age- and sex-specific HTLV-I prevalence in the general Japanese-American population, it is premature to recommend antibody testing of all such persons. Nevertheless, persons known to be infected with HTLV-I may be monitored for adult T-cell leukemia and HTLV-I–associated myelopathy/tropical spastic paraparesis with annual physical examinations and peripheral blood smears.

REFERENCES

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 1980; 77:7415-7419

2. Hinuma Y, Komoda H, Chosa T, et al: Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: A nation-wide sero-epidemiologic study. Int J Cancer 1982; 29:631-635

3. Clark JW, Gurgo C, Franchini G, et al: The molecular epidemiology of HTLV-I-associated non-Hodgkin's lymphomas in Jamaica. Cancer 1988; 61:1472-1482

4. Gessain A, Barin F, Vernant JC, et al: Antibodies to human T-lymphotropic virus type I in patients with tropical spastic paraparesis. Lancet 1985; 2:407-410

5. Rodgers-Johnson P, Gajdusek DC, Morgan OS, Zaninovic V, Sarin PS, Graham DS: HTLV-I and HTLV-III antibodies and tropical spastic paraparesis (Letter). Lancet 1985; 2:1247-1248

6. Murphy EL, Figueroa JP, Gibbs WN, et al: Sexual transmission of human T-lymphotropic virus type I (HTLV-I). Ann Intern Med 1989; 111:555-560

7. Okochi K, Sato H, Hinuma Y: A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: Seroconversion in recipients. Vox Sang 1984; 46:245-253

8. Manns A, Wilks RJ, Murphy EL, et al: A prospective study of transfusion transmission of HTLV-I and risk factors associated with seroconversion. Int J Cancer 1992; 51:886-891

9. Hino S, Yamaguchi K, Katamine S, et al: Mother-to-child transmission of human T-cell leukemia virus type-I. Gann [Jpn J Cancer Res] 1985; 76:474-480

10. Murphy EL, Blattner WA: HTLV-I-associated leukemia: A model for chronic retroviral diseases. Ann Neurol 1988; 23:S174-S180

11. Blattner WA, Nomura A, Clark JW, et al: Modes of transmission and evidence for viral latency from studies of human T-cell lymphotropic virus type I in Japanese migrant populations in Hawaii. Proc Natl Acad Sci USA 1986; 83:4895-4898

12. Wiktor SZ, Alexander SS, Shaw GM, et al: Distinguishing between HTLV-I and HTLV-II by western blot (Letter). Lancet 1990; 335:1533

13. Maeda Y, Furukawa M, Takehara Y, et al: Prevalence of possible adult T-cell leukemia virus-carriers among volunteer blood donors in Japan: A nation-wide study. Int J Cancer 1984; 33:717-720

14. Williams AE, Fang CT, Slamon DJ, et al: Seroprevalence and epidemiological correlates of HTLV-I infection in US blood donors. Science 1988; 240:643-646

15. Kline RL, Brothers T, Halsey N, Boulos R, Lairmore MD, Quinn TC: Evaluation of enzyme immunoassays for antibody to human T-lymphotropic viruses type I/II. Lancet 1991; 337:30-33

16. Tajima K, Tominaga S, Suchi T, Fukuta H, Komoda H, Hinuma Y: HTLV-I carriers among migrants from an ATL-endemic area to ATL non-endemic metropolitan areas in Japan. Int J Cancer 1986; 37:383-387

17. Ho GY, Nomura AM, Nelson K, Lee H, Polk BF, Blattner WA: Declining seroprevalence and transmission of HTLV-I in Japanese families who immigrated to Hawaii. Am J Epidemiol 1991; 134:981-987

18. Tsugane S, Watanabe S, Sugimura H, et al: Infectious states of human T lymphotropic virus type I and hepatitis B virus among Japanese immigrants in the Republic of Bolivia. Am J Epidemiol 1988; 128:1153-1161

19. Murphy EL: The epidemiology of HTLV-I: Modes of transmission and their relation to patterns of seroprevalence, *In* Blattner WA (Ed): Human Retrovirology: HTLV. New York, NY, Raven Press, 1990, pp 295-305

20. Murphy EL, Figueroa JP, Gibbs WN, et al: Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica—I. Demographic determinants. Am J Epidemiol 1991; 133:1114-1124

21. Ueda K, Kusuhara K, Tokugawa K, et al: Cohort effect on HTLV-I seroprevalence in Southern Japan (Letter). Lancet 1989; 2:979

22. Cruickshank JK, Richardson JH, Morgan OS, et al: Screening for prolonged incubation of HTLV-I infection in British and Jamaican relatives of British patients with tropical spastic paraparesis. Br Med J (Clin Res) 1990; 300:300-304

23. Hino S, Sugiyama H, Doi H, et al: Breaking the cycle of HTLV-I transmission via carrier mothers' milk (Letter). Lancet 1987; 2:158-159